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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/736,801	12/16/2003	Bert Klebl	DEAV2002/0089 US NP	4154

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EXAMINER	
HAMA, JOANNE	
ART UNIT	PAPER NUMBER
1632	

NOTIFICATION DATE	DELIVERY MODE
03/19/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/736,801	KLEBL ET AL.	
	Examiner	Art Unit	
	JOANNE HAMA	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 February 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,5-7,9,10,13-15,17,18,20 and 21* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,5-7,9,10,13-15,17,18,20 and 21* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on February 2, 2009 has been entered.

Per the Request for Continued Examination, the amendment submitted after the Final Action, July 7, 2008, will be considered.

Claims 2-4, 8, 11, 12, 16, 19, 22, 23 are cancelled. Claims 1, 18 are amended.

Claims 1, 5-7, 9, 10, 13-15, 17, 18, 20, 21, drawn to a method for generating a genetically modified yeast, are under consideration.

Withdrawn Objections/Rejections

Claim Objection

Applicant's arguments, see page 7 of Applicant's response, filed July 7, 2008, with respect to the objection of claim 23 have been fully considered and are persuasive. Applicant indicates that claim 23 is cancelled. The objection of claim 23 has been withdrawn.

New/Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 5-7, 9, 10, 13-15, 17, 20, 21 are newly rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1, step a, line 3 is drawn to "a detectable change of the phenotype." "The phenotype" lacks antecedent basis. Claims 5-7, 9, 10, 13-15, 17, 20, 21 depend on claim 1 and are included in the rejection.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 9, 10, 17, 18, 20, 21 remain rejected under 35 U.S.C. 102(b) as being anticipated by Chattopadhyay et al., 2000, Journal of Bacteriology, 182: 6418-6423, for reasons of record, April 10, 2007, January 4, 2008, August 12, 2008.

Applicant's arguments filed July 7, 2008 have been fully considered but they are not persuasive.

Applicant indicates that Chattopadhyay et al. do not teach all of the steps of claim 1 because there is no teaching or suggestion of amended claim 1 in Chattopadhyay et

al. Chattopadhyay et al. merely speculate that "...perhaps altered gene expression and modified vacuolar biochemistry contribute, at least in part, to maintaining a balanced cytosolic pH and maintaining cytosolic and vacuolar pH is important" (Applicant's emphasis, Chattopadhyay et al., page 6422, 1st col.). However, and most importantly, Chattopadhyay et al. go on to explain "(c)learly, this study has not completely addressed how btn1-Δ, with btn2-Δ and hsp30-Δ mutations, balances vacuolar pH (emphasis added, Chattopadhyay et al., page 6422, 1st col.). Thus, Chattopadhyay et al. have not teachings that a genetically modified yeast organism that is caused to express heterologously at least on protein or protein fragment by genetic modification by introducing a foreign gene into the yeast wherein the expression does not produce a detectable change of the phenotype, which is perceptible from the outside of said yeast organism. In response, this is not persuasive. Chattopadhyay et al. meet the limitations of the claims. As indicated in the Office Action of April 10, 2007, page 18, Chattopadhyay et al. teach that the BTN1 gene was disrupted in yeast, S. cerevisiae ("btn1-Δ"), and that no phenotype was seen in these yeast. DNA microarray results of btn1-Δ yeast indicate that two genes, HSP30 and BTN2, were upregulated. Chattopadhyay et al. teach that yeast comprising deletions of HSP30, BTN1, and BTN2 exhibited diminished growth at low pH (Chattopadhyay et al., page 6418, 2nd col., 2nd parag., also page 6420, 1st col.). As such, Chattopadhyay et al. meet the limitations of the claims. With regard to Applicant indicating that "...perhaps altered gene expression and modified vacuolar biochemistry contribute, at least in part, to maintaining a balanced cytosolic pH and maintaining cytosolic and vacuolar pH is important" and

"(c)learly, this study has not completely addressed how btn1-Δ, with btn2-Δ and hsp30-Δ mutations, balances vacuolar pH," indicating these citations do not address the 102 rejection at hand because regardless of Chattopadhyay et al.'s interpretation of their data, Chattopadhyay et al. teach the steps of claim 1 and thus, Chattopadhyay et al. anticipate the claims.

It is noted that the rejection of claim 23 is withdrawn as the claim is cancelled.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 5-7, 13 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over Chattopadhyay et al., 2000, Journal of Bacteriology, 182: 6418-6423 in view of Sauer, 1987, Molecular and Cellular Biology, 7: 2087-2096.

As discussed above, Chattopadhyay et al. teach a method of generating genetically modified yeast comprising the steps of disrupting BTN1, conducting a microarray study to determine that HSP30 and BTN2 were upregulated, and disrupting HSP30 and BTN2 expression in BTN1 null yeast.

However, Chattopadhyay et al. do not teach that the modified expression step is inducible.

At the time of filing, Sauer teach that the cre-lox site-specific recombination system was shown to function in an efficient manner in yeast. The cre gene, which codes for a site-specific recombinase, was placed under control of the yeast GAL1 promoter. lox sites flanking the LEU2 gene were integrated into two different chromosomes in both orientations. Excisive recombination at the lox sites (as measured by the loss of the LEU2 gene) was promoted efficiently by the Cre protein and was dependent upon induction by galactose (Sauer, abstract).

Therefore, it would have been obvious to take the cre-lox system taught by Sauer and to flank the endogenous BTN1 sequence with lox sites. An artisan would have done so in order to arrive at a yeast culture that can be split in half, wherein one half is induced with galactose. An artisan would then purify the mRNA from the galactose-induced and uninduced yeast and compared the mRNA expression between them in order to determine what genes were up- and downregulated following loss of BTN1 expression.

With regard to the claims being drawn to the knockout of the differentially expressed gene is carried out by replacing at least part of the coding sequence of the differentially regulated gene with the coding sequence of a reporter gene or parts of the reporter gene sequence (claim 13), Chattopadhyay et al. teach that to make the HSP30 and BTN2 knockout, part of the coding region for both genes was replaced by a URA3 gene (Chattopadhyay et al., page 6419, 1st col. under "Yeast strains, growth, and plasmids").

Thus, the claims are rejected.

Claims 1, 9, 10, 14, 15, 17-21 are newly rejected under 35 U.S.C. 103(a) as being unpatentable over DeRisi et al., 2000, FEBS Letters, 470: 156-160.

DeRisi et al. teach that Pdr1p/Pdr3p transcription factors render the cell resistant to chemical and nutritional stress in several ways other than the well-known regulation of ABC efflux transporters. After overexpressing Pdr1p and/or Pdr3p in S. cerevisiae and identifying upregulated and downregulated genes, DeRisi et al. teach that many of the genes overexpressed by the PDR1-3 and PDR3-7 mutations encode proteins that reduce intracellular accumulation of hydrophobic compounds, modulate enzymes involved in lipid synthesis and cell wall metabolism. DeRisi et al. teach that it would be interesting to investigate whether similar strategies for defense against noxious chemical agents are employed by other microorganisms, such as pathogenic yeasts (DeRisi et al., abstract and page 159, 2nd col., 3rd parag.).

While DeRisi et al. do not specifically teach that the upregulated genes in yeast overexpressing Pdr1p and/or Pdr3p were knocked out or that the downregulated genes were overexpressed, it would have been obvious for an artisan to knockout the upregulated genes and overexpress the downregulated genes in Pdr1p, Pdr3p or Pdr1p/Pdr3p yeast, such that an artisan would eliminate yeast that are resistant to chemical and nutritional stress. An artisan would have carried out the method in S. cerevisiae and adapted the treatment to pathogenic yeast.

With regard to the claims being drawn to the yeast not exhibiting a detectable change in phenotype (claim 1, step a), the yeast taught by DeRisi et al. do not have a

detectable phenotype as the morphology of the yeast is unaffected. In addition to this, DeRisi et al. can be interpreted to exhibit no detectable phenotype on the behavior of the organism when the detectable phenotype is defined to be rate of proliferation. However, the rate of proliferation would be affected in Pdr1p and/or Pdr3p yeast that comprise a deletion in an upregulated gene or in yeast that comprise a construct overexpressing a downregulated gene as the upregulated genes are drawn to genes involved in drug resistance (DeRisi et al., page 158) and genes that are downregulated are drawn to genes involved in transport of acids (DeRisi et al., page 159), which would affect the homeostasis of the yeast.

Thus, the claims are rejected.

Conclusion

No claims allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joanne Hama, Ph.D. whose telephone number is 571-272-2911. The examiner can normally be reached Mondays, Tuesdays, Thursdays, and Fridays from 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras, can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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/Joanne Hama/
Primary Examiner
Art Unit 1632